Med. Mycol. J.
Vol. 62, 29-34, 2021
ISSN 2185-6486

Original Article

Clinical Surveillance of Candidemia at Our Hospital

Akihiko Sano[1], Yoshifumi Nishi[2], Shota Yonetani[3], Hiroaki Yoshida[4], Hiroko Kawai[4], Shintaro Homma[5], Koji Araki[5], Yoko Ida[5], Hiroshi Makino[5], Daisuke Kurai[1], and Shin Kawai[1]

[1] *Department of General Medicine and Infectious Diseases, Kyorin University School of Medical*
[2] *Division of Medical Security and Patient Safety, Infection Control Room*
[3] *Faculty of Health Sciences, Kyorin University*
[4] *Department of Pharmacy, Kyorin University Hospital*
[5] *Department of Clinical Laboratory, Kyorin University Hospital*
*All author meet the ICMJE authorship criteria.

ABSTRACT

Treatment of Candidemia has become increasingly complicated as more and more non-*albicans Candida* species are being isolated in recent years.

We launched an investigation of the species, the MIC value, and the state of administration of antifungal drugs for all the cases with *Candida* spp. confirmed by blood cultures for the 7-year period from 2012 to 2018 at our hospital. In total, 192 cases were found and 206 strains of *Candida* species were isolated. Overall, 49.5% of the 206 isolated strains were *Candida albicans* (102 strains), followed by *Candida glabrata* (40 strains, 19.4%), and *Candida parapsilosis* (38 strains, 18.4%). The most frequently used antifungal drug for the initial dose was MCFG (120 cases, 59.2%), while the most frequently switched antifungal agent was L-AMB. Cases with an inappropriate end-of-treatment time represented 58.7% of all the cases.

We investigated the Candidemia situation at our hospital for a period of seven years. We believe that it is important for medical institutions to gather detailed data on candidemia at their own hospitals. Likewise, the hospital's Infection Control Team/Antimicrobial Stewardship Team should inform the physicians-in-charge about the appropriate diagnosis and treatment based on the data obtained.

Key words : candidemia, inappropriate therapy, non-*albicans Candida*, surveillance

Introduction

Candida remains a major nosocomial pathogenic microbe even with modern medicine. It ranks fourth among the pathogenic microbes that cause nosocomial bloodstream infections in the US[1)]. The mortality rate from Candidemia can reach as high as 20 to 50% [2-4)], though it varies depending on the counting method. Also, a delay in the initial treatment can result in an increase in the mortality rate according to reports[5)]. An appropriate treatment is therefore required. As for the composition of *Candida* spp. isolated from patients, non-*albicans Candida* species have been increasingly isolated globally [6, 7)]. About half of the *Candida* spp. isolated in Japan were *Candida albicans*[8)]. The Candidiasis Guideline issued by the Infectious Disease Society of America (IDSA)[9)] places importance on identification of species for selection of the treatment. We have been performing species identification of *Candida* spp. isolated from blood cultures obtained at our hospital since 2012. We studied the actual situation for seven years to obtain data to be fed back clinically. Herein we report the outcomes of our study.

Patients and methods

This study was conducted using data taken from patients hospitalised in Kyorin University Hospital in Tokyo, Japan. The data collection period is seven years from January 1, 2012 to December 31, 2018. All cases where *Candida* spp. was positive in blood cultures obtained from 18 years or older

Address for correspondence: Akihiko Sano, MD
Department of General Medicine and Infectious Diseases, Kyorin University School of Medical, 6-20-2 Shinkawa, Mitaka, Tokyo, 181-8611, Japan
Received: 25, May 2020, Accepted: 28, December 2020
E-mail: akihiko3133303@gmail.com

patients were included in the study, with an exemption of neutropenic cases according to the IDSA guideline. Our hospital is a general hospital attached to the Faculty of Medicine of Kyorin University having a total of about 1100 beds, of which ca. 100 beds are for critical cases. Isolation and identification of species of *Candida* spp. from blood cultures was performed using CHROMagar Candida and mass spectrometry (Multi TOF-MS). When a yeast-like fungus was isolated from the blood culture, the Micro-organism Test Room submits an initial report to the physician-in-charge. Within a few days (typically on the same or next day), the Infection Control Team (ICT) (which was renamed Anti-microbial Stewardship Team or AST in April 2018) examines the case to inform the physician-in-charge via the clinical record of the appropriateness of the drug for initial dose or the necessity of changing it; the necessity of retesting the blood culture, of seeking diagnosis by an ophthalmologist, and of removal of a device; the time of the end of treatment, etc. Any additional diagnosis or change of treatment was entrusted to the discretion of the patient's physician. For the measurement of the minimum inhibitory concentration (MIC) of different antifungal drugs of the isolated yeast-like fungi, ASTY kit for antifungal susceptibility (Kyokuto) was used. For the category, Clinical & Laboratory Standards Institute: CLSI M27-S4 was applied *mutatis mutandis*[10]. The target antifungal drugs were AMPH-B, MCFG, FLCZ, ITCZ, VRCZ, MCZ, and 5-FC. The number of the cases and the species, the MIC value, the treatment, and the prognosis were analysed and examined including for retrospective annual study. The cases with no treatment, no retesting of blood culture, or an end-of-treatment within 13 days after confirmation of blood culture-negative were defined as inappropriate treatment since an appropriate treatment could not be performed according to the guideline. However, any case of death within 14 days or less was excluded. As for the prognosis, a case of death within 14 days or less counting from the date when the blood cultures were collected was defined as an early death, while a case of death within 15 to 28 days was defined as a late death. Early death rate was computed by dividing the number of early death cases by the number of the survivors, and late death rate by dividing the number of late death cases by the number of the survivors. Any case where we could not confirm the patient's survival since he or she has left the hospital early or was transferred to another hospital was excluded from the computation. As there are some cases that are duplicated or have different times of occurrence, the number of the treatments and the prognosis was calculated based on the detected strains.

Results

1. Number of cases and their backgrounds

The total number of cases was 192, of which 120 were male (62.5%) and 72 were female patients. The average age of the patients was 56.2 ± 15.9, and the average serum albumin value was 2.4 ± 0.6 g/dl. The most common underlying disease of patients with positive case of candidemia was diabetes (50.0 %), followed by those with malignant tumours (40.8%), those receiving corticosteroid treatments (15. 5%), and those undergoing hemodialysis (11.2%). As for the number of cases by department, Critical Care Centre reported the highest number of cases (37), followed by Geriatric Medicine (internal medicine department for the aged) (32), Gastrointestinal Surgery (24), Gastroenterology (23), and Respiratory Medicine (17).

2. Number of strains

During the study period, 192 cases and 206 strains were detected. Overall, 49. 5% (102 strains) were *C. albicans*, followed by *Candida glabrata* (40 strains, 19.4%), *Candida parapsilosis* (38 strains, 18. 4%), *Candida tropicalis* (18 strains, 8.7%), *Candida guilliermondii* (5 strains, 2.4%), and other *Candida* spp. (3 strains, 1.5%). *C. albicans* and non-*albicans Candida* represented about half of the strains isolated (Fig. 1).

3. MIC

The MIC and the drug resistance of each type of strain were determined and compared against US CLSI (M27-S4). MIC data for the initial year were missing for *C. albicans*. Of the 40 strains of *C. glabrata*, only one strain was MCFG-resistant, which was found to possess an FKS gene mutation. One strain of *C. parapsilosis* was resistant to FLCZ, and three stains were susceptible-dose dependent (SDD). Non-susceptible strains represented 10.5% of all the strains. Three strains of (7.9%) were found to be resistant to VRCZ, an isogenic antifungal drug. For MCFG, the MIC was 2 μg/ml or less, and all strains were susceptible. For *C. tropicalis*, two strains (10.5%) were SDD to FLCZ, while six strains (33.3%) were SDD to VRCZ. One strain (5.6%) was found to be resistant to MCFG. FLCZ, VRCZ and MCFG were all inhibitory to *C. albicans* (Table 1).

4. Treatment

Data are represented by the number of the detected strains as there were redundant cases. Of all the antifungal drugs that were administered for the initial dose, MCFG was the most frequently used (120 cases, 59. 2%), followed by F-FLCZ/FLCZ (43 cases, 20.9%), L-AMB (18 cases, 8.7%), CPFG (2 cases, 1.0%), and VRCZ (1 case, 0.5%). Twenty-two cases (10. 7%) were not treated at all. As for the

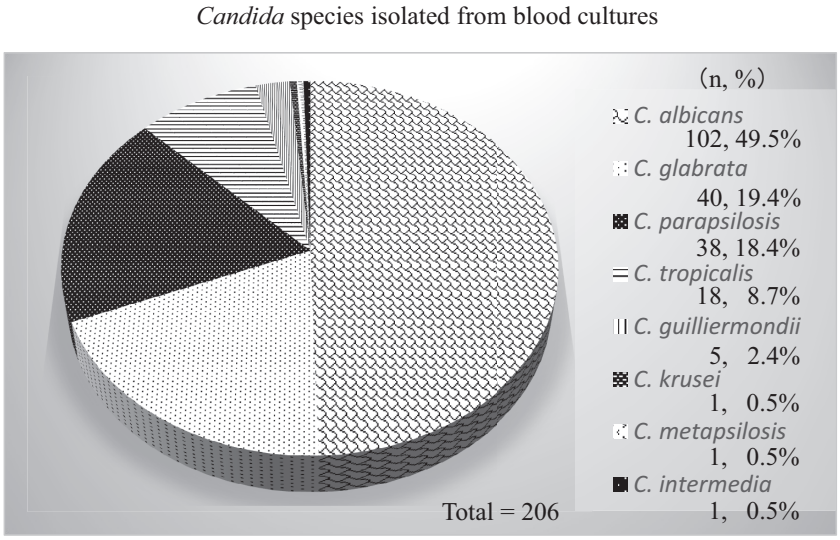

Fig.1. *C. albicans* strains represent almost half of the isolated strains, followed by *C. glabrata* and *C. parapsilosis*.

Table 1 Minimum inhibitory concentration (μg/ml) of *Candida* species

	No. of strains	MIC (μg/ml)												
		0.02	0.03	0.06	0.13	0.25	0.5	1	2	4	8	16	32	64
FLCZ														
C. albicans	96		1			69	24	2						
C. glabrata	40								2	1	9	21	6	1
C. parapsilosis	38					1	7	15	11	3	1			
C. tropicalis	18						4	7	5	2				
C. guilliermondii	5									1	3	1		
VRCZ														
C. albicans	96		1			69	24	2						
C. glabrata	40			1	1	8	23	6	1					
C. parapsilosis	38					1	7	15	11	3	1			
C. tropicalis	18						4	7	5	2				
C. guilliermondii	5									1	3	1		
MCFG														
C. albicans	96		75	17	4									
C. glabrata	40		35	4				1						
C. parapsilosis	38				1	4	9	18	6					
C. tropicalis	18		5	12				1						
C. guilliermondii	5					2		2	1					
AMPH-B														
C. albicans	96					6	83	7						
C. glabrata	40						24	16						
C. parapsilosis	38					1	24	13						
C. tropicalis	18						11	7						
C. guilliermondii	5						5							

Only MIC data of *C. albicans* for the year 2012 were not available.

Table 2. The most frequently initial therapy was MCFG. The most switched therapy was L-AMB

	Antifungal agents			
	Initial therapy n (%)		Switched therapy n	
MCFG	120	(58.7)	L-AMB	23
			F-FLCZ	17
			FLCZ-PO	2
			VRCZ-DIV	4
			CPFG	2
L-AMB	18	(8.7)	MCFG	4
			F-FLCZ	4
			VRCZ-DIV	1
F-FLCZ/FLCZ	43	(20.7)	MCFG	16
			L-AMB	4
CPFG	2	(1.0)		
VRCZ	1	(0.5)		
no treatment	22	(10.6)		
Total	206			

breakdown of the antifungal drugs that were switched from the initial dose, MCFG was switched to L-AMB in 23 cases and to F-FLCZ in 17 cases. L-AMB was switched to MCFG in 4 cases and to F-FLCZ in 4 cases. F-FLCZ/FLCZ was switched to MCFG in 16 cases and to L-AMB in 4 cases (Table 2).

Though it is recommended by the IDSA Guideline to retest blood cultures and provide treatment for 14 days after turning to negative, blood cultures were retested in only 138 cases (67.0 %), while the treatment was ended after turning to negative in 106 cases (50. 0%). Antifungal drugs were continuously administered for at least 14 days from the time of the confirmation of turning to negative in 50 cases (24.3%). Inappropriate treatments were found in a total of 108 strains at an average of 52. 4%. The percentage of inappropriate treatments annually was 58.6% in 2012, 69.7% in 2013, 51.2 % in 2014, 51.9% in 2015, 46.7% in 2016, 46.2% in 2017, and 38.7% in 2018.

Discussion

According to a global surveillance report by Pfaller et al., while *C. albicans* represented 73.3% of all the *Candida* spp. in 1997, the frequency of identification of *C. albicans* decreased to 65. 0% in 2007, and non-*albicans Candida* tended to increase[6, 7]. According to the data reported by Morii et al. regarding the frequency of occurrence in Japan during the period from 2004 to 2011, the rate of occurrence of *C. albicans* decreased to 43.3%. The frequency of identification of non-*albicans Candida*, however, is somewhat different from the data at our hospital. The data obtained at our hospital shows that the frequency of isolation of *C. albicans* is about 50%, the frequency of *C. glabrata* and that of *C. parapsilosis* are at a similar level, only one strain of *Candida krusei* was identified for the 7-year period, and no *Candida lusitaniae* was detected so far.

As for the antifungal drug susceptibility, MCFG is the most frequently used due to its high clinical safety. However, we should be pay attention to the fact that one strain of *C. glabrata* possessing an FKS gene was isolated at our hospital. Administration of an echinocandin antifungal drug is not recommended for treatment of *C. parapsilosis* by the IDSA[9, 11] or the guideline for diagnosis and treatment of deep mycosis released in Japan in 2014[12] because of the risk of existence of strains that show a higher MIC. However, the minimum inhibitory concentration (MIC) to MCFG at our hospital was no more than 2 μg/ml in all cases according to the decision criterion based on CLSI breakpoint MIC[10]. Rather, it is not recommended to use this drug as the resistance of *C. parapsilosis* to fluconazole (FLCZ) is 10. 5% and that to voriconazole (VRCZ) is 7.9% respectively, both of which are azole antifungal drugs. With regard to *C. guilliermondii*, little data are mentioned in the IDSA, while use of liposomal amphotericin B (L-AMB) and VRCZ instead of MCFG is recommended by the Japanese guideline. However, all of the five strains isolated at our hospital were susceptible to this drug. Though it is not categorized, the MIC of VRCZ is no more than 0. 5 μg/ml, so it is used clinically. As for *C. tropicalis*, 10.5% were SDD to FLCZ, the drug of first choice, while 33.3% were SDD to VRCZ, the drug of second choice. Thus, neither of these drugs is recommended at our hospital. A therapeutic effect of MCFG can be expected as its MIC is 0.06 μg/ml. This hypothesis is primarily based on studies on blood culture-positive cases and thus does not take into account the actual year-on-year increase of cases of prophylactic administration of VRCZ through ingestion at our hospital for examination of the observed severe susceptibility of *C. tropicalis* to VRCZ. Such cases increased to 73.5% in 2015, 72.5% in 2016, 75.5% in 2017, and eventually to 82.1% in 2018, which can be the cause of the severe susceptibility, pointing to the need for further research. Since the information on drug sensitivity provided in the guidelines does not always coincide with the study outcome at each institution; as mentioned above, it is important to aggregate the data on the frequency of isolation and the MIC at each institute when creating the antibiogram.

If we compare ACTIONs Bundle data[13] with the data obtained at our hospital, we used echinocandin antifungal drugs as frequently as in ACTIONs Bundle, but chose to administer MCFG in majority of the cases (MCFG in 120 cases/CPFG in 2 cases). This was due to our abundant experience of using this drug and to the fact that the MIC of

CPFG could not be measured until 2017 at our hospital. Consequently, however, we found no certainty in the MIC of CPFG even after the measurement became available. The somewhat frequent use of L-AMB as the drug of first choice other than candin antifungal drugs reflects a difference of whether L-AMB, which demonstrates wide-range antifungal action from an early stage, was used as a drug of first choice, or switching to L-AMB was determined because of a poor therapeutic effect of another drug in the early treatment. At our hospital, the ICT (or AST) recommended the administration of L-AMB to physicians-in-charge to save lives in many cases.

As the cases of contamination by other fungi in Candidemia is extremely low[14], and the mortality is high, it is recommended to promptly start an appropriate treatment of any positive case. As for the treatment period, a 14-day treatment should be performed counting from the date of confirmation of blood culture-negative when retesting the blood culture after the start of an appropriate treatment in line with the IDSA and the Japanese guidelines. The cases with inappropriate treatment at our hospital represent an average of 52. 4% for the 7-year period, which points to room for improvement. However, such cases tend to decrease according to the annual data.

In conclusion, the clinical surveillance of candidemia at our hospital for seven years revealed that 206 strains were detected including roughly 50% *C. albicans*. We created our own antibiogram of *Candida* spp. for candidemia at our hospital. MCFG was the most frequently used initial dose of antifungal drug, and L-AMB the most frequently chosen alternative. Inappropriate treatment rates were at an average of over 50%, but the rates have decreased gradually. We believe that it is important for medical institutions to gather detailed data on candidemia at their own hospitals. Likewise, the hospital's ICT/AST should inform the physicians-in-charge about the appropriate diagnosis and treatment based on the data obtained.

Conflicts of interest

Non to declare.

Ethical approval

This surveillance was conducted with the approval of the ethics committee of Kyorin University School of Medicine (No.1329)

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